REMARKS

Claims 1 – 10 and 12 – 14 are pending and under consideration. Claims 11 and 15 were previously canceled. With this Amendment, claims 1, 4, 9 and 10 are being amended, and claims 6 – 8 are being canceled without prejudice against their reintroduction into this or one or more timely filed continuation, divisional or continuation-in-part applications, and claims 16 – 23 are being newly added. Thus, after entry of this Amendment, claims 1 – 5, 9 – 10, 12 – 14, and 16 – 23 are pending and under consideration. The amendments to the claims and specification and the various rejections raised in the Office Action are discussed in more detail, below.

The Amendments to the Claims

Claim 1 has been amended to limit the clinical indication to head pain conditions involving a cerebral vasodilatation mechanism, including primary and secondary headache disorders, and to limit the substituent, "R", to an optionally substituted phenyl group. A consequential amendment to claim 4 has been made to delete the single species of the Markush group that is inconsistent with the amendment to claim 1, from which claim 4 depends. Claims 9 and 10 have been amended to delete reference to neuralgias, and claim 10 has been further amended for clarity.

Each of new claims 16 – 18 is drawn to a specific species recited in the Markush group of claim 5, from which each of the new claims directly depends.

Support for new claim 19, which limits the treated mammal to human, is found particularly at page 7, line 15.

New claim 20, which depends from claim 1, further specifies that the pharmaceutically acceptable derivative is an acid addition salt. Support for this claim may be found in the specification notably at page 9, first full paragraph (lines 6 – 13).

New claim 21, which depends directly from claim 1 and further specifies oral administration, and new claim 22, which specifies parenteral administration, find support

throughout the specification, for example at page 9, beginning at the third full paragraph, and continuing to page 11, fourth full paragraph.

Support for new claim 23, which limits the disorder of cerebral vasodilatation to migraine, can be found throughout the specification.

No new matter has been added by virtue of these amendments.

The amendments to the specification

Several amendments are being made to bring this European-originated specification into compliance with U.S. practice.

The CROSS-REFERENCE TO RELATED APPLICATIONS, first added in applicants' preliminary amendment, has been amended additionally to recite the foreign priority claim to European patent application no. 03000921.1, filed January 16, 2003, a priority claim that was originally set forth in the international application of which the instant application is the U.S. national stage under 35 U.S.C. § 371.

The paragraph on page 3, lines 2 – 8, has been amended to ensure that the language comports with the statement found later in the specification, in the fourth full paragraph at page 16, which reads in relevant part: "The above data confirm that ***representative*** substituted 2-aminoacetamide compounds disclosed in WO99/26614 are not effective as antimigraine agents. . . ." (emphasis added).

A redundant word has been deleted for clarity from the third full paragraph on page 3.

The first paragraph on page 12, lines 1 – 6, has been amended to correct verb tense in accordance with U.S. practice, and more closely to comport with the data shown.

No new matter has been added by virtue of these amendments.

Election of species

In the Amendment and Response to Restriction and Election of Species Requirement filed November 19, 2007, prior counsel of record provisionally elected 2-[4-(2-fluorobenzyloxy)benzylamino]-propanamide as that species of α-aminoamide to which examination would be restricted if no claim generic thereto were found allowable, 37 C.F.R. § 1.146, and traversed the requirement on the ground that "Applicants submit that the individual compounds of formula (I) are not patentably distinct, as the compounds all have 'analgesic activity . . . , in particular against chronic and neuropathic pain in mammals' (specification, page 7, lines 13 – 15)."

Applicants' traversal appears to have been improper: "analgesic activity . . . , in particular against chronic and neuropathic pain in mammals" does *not* speak to the invention described and claimed in the instant application, treatment of head pain conditions involving a cerebral vasodilatation mechanism, such as migraine. Instead, the portion of the specification that applicants quoted in support of the alleged patentable indistinctness of the various species speaks to *earlier* inventions, methods of using the compounds in treating clinical indications[1] which do not predict efficacy in the therapeutic methods presently claimed. The referenced section of the specification reads as follows:

> The α-aminoamides of formula (I) and the analgesic activity thereof, in particular against chronic and neuropathic pain in mammals including humans, are disclosed in WO90/14334, W094/22808, WO97/05102, WO99/26614, WO99/35123 and WO99/35125; any of the α-aminoamides of the above formula (I) can be prepared according to what [is] disclosed in said documents which are herein incorporated by reference as far as the preparation of said α-aminoamides is concerned.
>
> W090/14334, WO94/22808, WO97/05102, W097/05111, disclose substituted benzylaminoamide compounds active on the central nervous system and useful as anti-epileptic, anti-Parkinson, neuroprotective, antidepressant, antispastic hypnotic agents

[1] Including chronic and neuropathic pain, epilepsy, Parkinson's disease, neural injury, depression, spasticity, acute and chronic pain.

(Pevarello P., Bonsignori A., Doster[t] P., Heldempergher F., Pinciroli V., Colombo M., McArthur R.A., Salvati P., Post C., Fariello R.G. and Varasi M.: "Synthesis and anticonvulsant activity of a new class of derivatives", J. Med. Chemistry 1998, 41: 579-590).

As discussed in further detail below, efficacy in treating disorders of cerebral vasodilatation, such as migraine, as presently claimed, cannot be predicted solely from the prior art demonstration of efficacy "against chronic and neuropathic pain". Accordingly, the prior disclosures referenced by the applicants in their traversal cannot properly speak to the patentable distinctiveness of the various species of α-aminoamide in the therapeutic methods of applicants' now-claimed invention; the alleged basis for applicants' earlier traversal is simply not relevant to the necessary inquiry.

Accordingly, applicants here reaffirm the provisional election of 2-[4-(2-fluorobenzyloxy)benzylamino]-propanamide as that species of α-aminoamide to which examination should be restricted if no claim generic thereto were found allowable, 37 C.F.R. § 1.146, and invite the Examiner, in light of this discussion, to revisit the Election of Species as the Examiner deems appropriate.

Rejection Under 35 U.S.C. § 112, first paragraph, scope of enablement

Claims 1 – 10 and 12 – 14 have been rejected under 35 U.S.C. § 112, ¶ 1, on the ground that the specification does not enable the use of the entire genus of compounds recited in claim 1 in the claimed methods of treatment.

The Examiner acknowledges that the claimed methods are fully enabled across the genus of "compounds of formula I wherein R is a phenyl ring, unsubstituted or substituted by one or two substituents independently selected from halogen, hydroxy, C1-C4 alkyl, C1-C3 alkoxy and trifluoromethyl." Office Action at page 3.[2] Solely to expedite prosecution, and without thereby acceding to the accuracy or adequacy of the Examiner's *prima facie* case of nonenablement,

[2] Although claims 1 – 10 and 12 – 14 are said to be rejected, the rejection should not properly have been applied to claims 2, 3, and 5 as examined, each of which limits R to an optionally-substituted phenyl ring.

applicants herein amend the claims, all of which now limit R to an optionally-substituted phenyl ring. Accordingly, the rejection has been obviated, and should be withdrawn.

Rejections Under 35 U.S.C. § 102(b) and §103

Claims 1 - 4, 6 - 10, 12, and 13 – which as examined had been drawn to "method[s] of treating head pain conditions" – stand rejected under 35 U.S.C. § 102(b) as anticipated by Pevarello *et al.*, WO 99/35125 ("Pevarello"). Pevarello is said by the Examiner to

> teach[ ] compounds of formula I . . . as therapeutic agents used for treating pain associated with damage or permanent alteration of the peripheral or central nervous systems such [as] peripheral neuropathies e.g. trigeminal and post-therapeutic neuralgia, diabetic neuropathy, glossopharyngeal neuralgia, radiculopathy, neuropathy secondary to metastatic infiltration, adipossis dolorosa and burn pain and central pain conditions such as those following stroke, thalamic lesions and multiple sclerosis (page 6, lines 13-22).

Office action at page 8. The Examiner contends that "the limitations of claims 1 – 4 and 7 – 10 are [thereby] met." Office Action, at page 8. With respect to claim 6, which as examined had depended from and further limited claim 1 to treatment of head pain conditions "wherein the head pain conditions are involving a cerebral vasodilatation mechanism," the Examiner further contends that the further limitation "is not of patentable weight. Pain is pain, no matter the mechanism by which it occurs, thus meeting the limitations of claim 6." Office Action, at page 8. Pevarello is also said to disclose dosage regimens that anticipate claims 12 and 13.

The rejections have been obviated by amendment of claim 1, the sole independent claim, which is now drawn to "a method of treating head pain conditions involving a cerebral vasodilatation mechanism."[3] The rejections, having been obviated, should be withdrawn.

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[3] Although head pain is a *symptom* of disorders involving a cerebral vasodilatation mechanism, such as migraine, the treatment of the underlying etiology is not synonymous with "treatment of head pain", any more than treatment of cardiac ischemia is synonymous with treatment of chest pain, or treatment of bone cancer is synonymous with treatment of bone pain.

Rejections Under 35 U.S.C. § 103

Claim 5, which further limits the method of claim 1 to the administration of three species of α-aminoamide compounds, is rejected as having been obvious over Pevarello. The rejection has been obviated by the amendment to claim 1; claim 5 is now drawn, by dependency, to *treatment of head pain conditions involving a cerebral vasodilatation mechanism* through the administration of an α-aminoamide selected from the group consisting of:
(S)-(+)-2[4-(3-fluorobenzyloxy)benzylamino]-propanamide,
(S)-(+)-2-[4-(2-fluorobenzyloxy)benzylamino]-propanamide and
(S)-(+)-2-[4-(3-chlorobenzyloxy) benzylamino]-propanamide.

Claim 14, which recites a dosage range of 0.5 to 5 mg/kg day, stands rejected under 35 U.S.C. § 103 as having been obvious over Pevarello, further in view of Lan (WO 99/26614); the secondary reference is said to teach "a dosage regimen for said compounds ranging from 0.0025 to 50 mg/kg." Office action at page 11. "Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have employed the 2-aminoacetamides compounds taught by Pevarello in the dose ranges taught by Lan." Office Action, page 11.

With the claims now drawn exclusively to methods of treating disorders of cerebral vasodilatation, head pain conditions involving a cerebral vasodilatation mechanism, rather than to methods of treating pain, the rejection has been obviated, and should be withdrawn.

However, the Examiner further notes that Lan "discloses . . . the treatment of a number of ailments including migraine headaches (page 7, line 22 – page 8, line 3)," Office Action, page 11. On that basis, the Lan disclosure, alone or in combination with Pevarello, might be argued to have relevance to the patentability of applicants' claims as herein amended. Accordingly, to expedite prosecution, applicants offer the following comments.

First, the Lan disclosure is more properly characterized as having ***suggested***, rather than ***disclosed***, "the treatment of a number of ailments including migraine headaches." In interference

no. 105,394, the Board of Patent Appeals and Interferences held that the Lan disclosure did not enable methods of treating or ameliorating pain:[4]

> On the issue of enablement, we conclude that Pevarello has met its burden of proof that Lan's specification fails to provide an enabling disclosure for Lan's involved claims. In particular, we have credited the testimony of Dr. Waxman, Pevarello's expert, who testifies that one of ordinary skill in the art would not have accepted Lan's specification as providing a basis for concluding that Lan's compounds would reasonably have been expected to be useful in treating or ameliorating pain.
>
> * * *
>
> Lan no longer has any patentable claims corresponding to the count and lacks an enabling disclosure of a method of treating or ameliorating pain, which is required by the count.[5]

Although the Board spoke in its Decision only to the then-claimed subject matter, methods of treating or ameliorating pain, there is simply no evidence that any other of the myriad clinical indications listed by Lan would have been enabled by Lan's scant *in vitro* data. At most, then, Lan ***suggests*** that the reader try the 2-aminoacetamide compounds disclosed therein to assess their potential in treatment of migraine.

Notwithstanding any such suggestion, there would have been no reasonable expectation that the compounds would in fact have proven efficacious in treating disorders of cerebral vasodilatation, such as migraine. As noted in applicant's specification,

> [i]t is . . . known that headache resulting from neurovascular mechanisms does not satisfactorily respond to treatment with analgesic agents and, conversely, antimigraine compounds, such as

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[4] The Lan application that was involved in interference no. 105,394, application serial no. 10/429,764, was an application to reissue Lan's U.S. Pat. No. 6,479,484, which issued from application no. 09/554,739; the '739 application was the U.S. national phase under 35 U.S.C. § 371 of PCT/US98/24965, which published as the WO 99/26614 ("Lan"). Thus, the disclosure to which the Board's decision and judgment were addressed is the same as the disclosure of the Lan PCT publication relied upon by the Examiner here. Copies of the Decision and Judgment are filed concurrently herewith as part of applicant's Supplemental Information Disclosure Statement.

[5] DECISION – PRELIMINARY MOTIONS – Bd. R. 125. Enclosed herewith.

triptans, do not possess general analgesic properties (Steiner T.J., Findley L.J., Yuen A.W.: "Lamotrigine versus placebo in the prophylaxis of migraine with and without aura", Cephalgia 1997, 17: 109-12; Saxena P.R., Den Boer M.O.: "Pharmacology of antimigraine drugs", J. Neurology 1991, 238 Suppl. 1: S28-35); therefore, the antimigraine properties cannot be predicted on the basis of pain models.

Specification, pp. 2 – 3. Furthermore, using an animal model that is, by contrast, well-accepted to predict efficacy in treatment of migraine, the present applicants demonstrated that an exemplary Lan compound, 2-(4-(2-fluorobenzyloxy)benzylamino)-2-methyl-propanamide (NW1050), was ineffective at inhibiting cerebral blood flow evoked by electrical stimulation of the left ophthalmic branch of the trigeminal ganglion (see Table 1, page 15).

Accordingly, applicants respectfully submit that the claims as herein amended would not have been obvious over Lan, alone or in combination with Pevarello, and that no rejection of the present claims under 35 U.S.C. § 103 would be proper.

Conclusion

Claims 1 – 5, 10, 12 – 14, and 16 – 23 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly requested. No fees beyond those due for extension of time are believed to be due in connection with this Amendment. However, the Director is authorized to charge any additional fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 **(Order No. 373987-004US (396982)).**

Respectfully submitted,

Date: MAY 21, 2008

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